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Docket No. 1004316.009US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Masataka KUWANA, et al.	Confirmation No.:	2198
Serial No.:	10/549,707	Group Art Unit:	1649
Filed:	October 27, 2005	Examiner:	Dutt, Aditi
For:	MONOCYTE-ORIGIN MULTIPOTENT CELL MOMC		

ARGUMENTS SUPPORTING PRE-APPEAL BRIEF REQUEST FOR REVIEW

Commissioner for Patents
P.O. Box 1450
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Sir:

In response to the Non-Final Official Action mailed July 20, 2009, wherein Claims 2-8 have been twice rejected under 35 U.S.C. §102(b) as being anticipated by Zhao, et al. (*PNAS,* 100: 2426-2431, 2003), the applicants file herewith a "Notice of Appeal" along with a "Pre-Appeal Brief Request for Review (PTO/SB/33 Form). These arguments are being submitted herewith to support the Pre-Appeal Brief Request for Review.

Remarks/Arguments begin on page 2 of this paper.

REMARKS

In July 20, 2009 Non-Final Office Action, claims 2-8 have been rejected under 35 U.S.C. §102(b) as being anticipated by Zhao, et al. (*PNAS,* 100: 2426-2431, 2003). In essence, the Patent Office concludes that since "PSC of Zhao et al. and the instant MOMC, both being multipotent or pluripotent stem cells, both having derived from the same source and expressing the same markers, have similar differentiation potential . . . the cells of the prior are would be functionally the same under identical culture conditions [as the claimed cells]." (Office Action, pgs. 9-10). Relying on this evidence, the Patent Office concludes that Zhao "clearly" anticipates the claimed invention (Office Action; pg. 4). Applicants respectfully disagree and assert that the Patent Office's rejections are based upon clear errors in facts and lack the essential elements to establish a *prima facie* rejection.

(1) The instant claims are directed to the adult stem cells with multidifferentiation potential derived from the circulating $CD14^+$ monocytes. These novel cells are known in the art as the "monocyte-derived/originated multipotent cells (MOMC)." (See Kuwana, et al. "Human circulating CD14+ monocytes as a source of progenitors that exhibit mesenchymal cell differentiation," *Journal of Leukocyte Biology* **2003**; 74:833-845; and Kuwana, et al. "Endothelial differentiation potential of human monocyte-derived multipotential cells," *Stem Cells* **2006**, 24(12):2733-2743; both already cited).

Conventionally, a combination of multiple markers (distinctive phenotype) and a differentiation potential is used to identify a particular stem cell type. (*Stem Cell Report*; NIH June 2001 cited by the Examiner; in particular see Appendix E.i "How Do Researchers Use Markers to Identify Stem Cells?). In case of MOMCs, these cells have the distinctive phenotype positive for CD14 (a monocyte marker), CD34 (a stem cell marker), CD45 (a hematopoietic cell marker), type-I collagen (a mesenchymal cell marker), and HLA-DR markers (a human

leukocyte antigen) (Claim 2). A combination of these markers helps one of ordinary skill in the art to identify the MOMC cells and distinguish them from any other cells type. However, in addition to a distinctive phenotype, the MOMC cells also have a unique differentiation potential. For instance, the MOMC cells can differentiate, among others, into osteoblasts, skeletal myoblasts and chondrocytes.

(**2**) The Patent Office refutes this standard of defining a novel type of the isolated stem cells and puts forward an argument that the PSC cells (pluripotent stem cells) of Zhao anticipate the claimed invention, i.e., MOMC cells, because "PSC of Zhao et al. and the instant MOMC, both being multipotent or pluripotent stem cells, both having derived from the same source and expressing the same [sic, similar] markers, have similar differentiation potential . . . [and] Zhao's PSC are structurally the same as MOMC, therefore, the cells of the prior are would be functionally the same under identical culture conditions." (emphasis added by the applicant). However, such an argument is without merit and contrary to a well established view in the art.

Applicants do not refute that because MOMC and PSC come from the same source, i.e., circulating $CD14^+$ monocytes, there are some similarities between these two cell types. But that is also true between many related cells. For instance, the similarities between macrophages and dendritic cells are quite substantial because they are both derived from the monocytes (e.g., $HLA\text{-}DR^+$, $CD34^-$, Type-I $collagen^-$, etc.), yet it is well recognized in the art that these are very different cells (e.g., see Table 2 of Kuwana **2003**). Following the logic of the Patent Office, since under identical environmental cues monocytes will turn only into macrophages, or vise versa, monocytes will turn only into dendritic cells, macrophages and dendritic cells, therefore, must be the same, which is incorrect. The same can be said about the stem cells during the embryonic development, where due to environmental cues the cells can go from totipotent, to pluripotent, multipotent and finally unipotent progenitors that form pancreas, muscles, bones,

etc.. These are different cells, yet related by originating from the same source. By the same token, merely because there are similarities between PSC and MOMC and they come from the same source does not make them the same.

As applicants explained in the August 29, 2008 and February 7, 2008 Responses and in the Declaration under 37 CFR § 1.132 by Dr. Kuwana, MOMC cells can be readily distinguished from the PSC cells of Zhao based on its phenotype and differentiation potential. In fact, applicants previously cited a peer-reviewed publication by Seta, et al. "Human circulating monocytes as multipotential progenitors," *Keio J Med* **2007**, 56(2):41-47 (see Table 1), which discusses how the two cell types are different and distinguished. (See Response dated February 7, 2008 at pages 8-9). For instance, Seta states that "[t]hese monocyte-derived cells commonly have spindle-shaped morphology and express CD45 and CD34, but have several distinct characteristics. PSC[s] . . . are able to self-replicate and expand in long-term cultures, whereas MOMC have limited lifespan." (Seta; pg. 45; Table 1).

Moreover, as explained in the February 16, 2009 Response, Zhao teaches that the PSC cells have low expression of the human leukocyte antigen HLA-DR (RFI ~18), whereas the macrophages (s-MΦ) have a high expression of the HLA-DR (RFI ~106). In comparison, the expression of the HLA-DR in the MOMC is the same as in the macrophages, *i.e.*, high/strong. (See Table 2 of Kuwana; ++ - strong staining for both). Taken together, this clearly indicates that MOMC and PSC have different HLA-DR expression and in MOMC, HLA-DR can be used as a distinctive phenotype. On the other hand, Zhao teaches away from using HLA-DR marker to identify PSC because this is essentially, in combination with other identifiers, how Zhao characterizes macrophages and distinguishes them from PSC cells. (Zhao et al., page 2428, left column, line 24 – right column, line 3). Even though PSC expresses some HLA-DR, Zhao uses this marker to demonstrate a transformation of PSC cells into the macrophages (low HLA-DR →

high HLA-DR). Hence, one of skill in the art would not use HLA-DR as a distinctive marker of the PSC cells, whereas, HLA-DR is a distinctive marker of the MOMC cells (Claim 2).

Finally, in Table 1, Seta also demonstrates that two cell types have distinguishable differentiation potential, which is expressly presented in the claims (See Claim 2). Specifically, MOMC cells differentiate into osteoblasts, skeletal myoblasts, or chondrocyte, whereas PSC cells of Zhao do not. On the other hand, PSCs of Zhao differentiate into macrophages, T-lymphocyte, Epithelial cells, and Hepatocytes, whereas the instant MOMC cells do not. If the MOMC and PSC cells are the same as proposed by the Examiner, then applicants should have been able to differentiate MOMC cells based on Zhao's methods and arrived at the same results. However, as shown in the declaration by Dr. Kuwana, the induction of MOMC cells with IL-2, NGF, EGF and HGF did not produce the differentiated cells of Zhao, clearly suggesting that the claimed cells are different from Zhao.

Thus, considering the framework within which the invention must be examined and measured, *i.e.*, a distinctive phenotype (CD14, CD34, CD45, type-I collagen, and HLA-DR) and a unique differentiation potential (osteoblasts, skeletal myoblasts, or chondrocyte), as a matter of law (See MPEP 2131) Zhao does not anticipate the claimed invention because each and every element as set forth in the claim is **not** found, either expressly or inherently, in Zhao.

(**3**) The Patent Office states "although the reference [Zhao] is silent on the expression of collagen type I, this would be an inherent characteristic because the cells are derived from monocytes isolated from the peripheral blood mononuclear cells" (Office Action; pg. 4). To support this assertion, the Patent Office looks to He et al. (*Stem Cells* 25: 69-77, 2007; page 73, col 1, para 1) to conclude that PSC cells of Zhao must have Type-I collagen marker because they resemble fibroblasts and because they have similar morphology and phenotype. (Office Action dated August 10, 2007; pg. 4). However, this assertion is incorrect.

"The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." *In re Rijckaert*, 9 F.3d 1531, 1534, (Fed. Cir. 1993) (cited in MPEP 2112). The attention of the Patent Office is respectfully directed to page 46 and Table 1 of Seta et al. The reference describes the monocyte-derived EPC cells extracted from the peripheral blood mononuclear cells that proliferate into osteoblast (bone), adipocyte, endothelial cell and neural cells. These cells also have similar fibroblast morphology and phenotype to PSC, MOMC and fibrocyte cells (see Table 1 of Seta). Nonetheless, these cells are negative for the type-I collagen marker, so are the monocytes, macrophages and dendritic cells (see Table 2 of Kuwana, 2003). In the relevant art, the presence of type-I collagen is considered a distinctive phenotype marker. For instance, in the description of the fibrocyte, Seta states that this cell "was characterized by its distinctive phenotype positive for CD45, CD34, and type I collagen." (emphasis added; Seta; pg. 46, col. 2, para. 2). If, as suggested by the Patent Office, the type I collagen marker was inherent in monocytes isolated from the peripheral blood mononuclear cells, then the monocytes themselves should be positive for this marker, but they are not. Moreover, one skilled in the art would not and could not consider this marker as a "distinctive phenotype" for stem cells if it is so prevalent. Thus, the argument put forth by the Patent Office that the phenotype positive for type-I collagen marker is inherent in PSC is based on the unsubstantiated hypothesis of the Examiner and goes against the available evidence and utilization of such phenotype as a distinctive marker for the unique adult stem cells. Inherency "may not be established by probabilities and possibilities." (MPEP 2112).

Applicants respectfully submit that at least for the aforementioned reasons, claims 2-8 are not anticipated by Zhao because Zhao does not disclose each and every element of the claims as presented herewith (See MPEP 2131). Reconsideration and withdrawal of the rejections under 35 U.S.C. §102(b) of claims 2-8 as being anticipated by Zhao, et al. are respectfully requested.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **50-4827**, Order No. 1004316.009US.

Respectfully submitted,
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